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Dichlorvos Exposure and Human Cancer Risk: Results from the Agricultural Health Study

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Abstract

Objectives—We evaluated cancer risk from DDVP (2,2-Dichloroethenyl dimethylphosphate) exposure among pesticide applicators enrolled in the Agricultural Health Study (AHS) cohort.

Methods—The AHS is a cohort of 57,311 pesticide applicators in North Carolina and Iowa, enrolled from 1993–1997 and followed for cancer through 2004. A comprehensive questionnaire collected information on exposure to DDVP and potential confounders. Among the 49,762 licensed pesticide applicators eligible for analysis, 4,613 reported use of DDVP. DDVP exposure was classified as intensity-weighted cumulative exposure days (IWED), calculated as [years of use × days per year × intensity level]. Poisson regression analysis was used to calculate rate ratios (RR) and 95% confidence intervals (CI) to evaluate the association of DDVP exposure among 2,943 incident cases of cancer.

Results—DDVP exposure was not associated with any cancer studied here. We observed no elevation in risk among lymphohematopoietic cancers, RR = 1.00 (95% CI 0.51, 1.96) and a small excess risk associated with exposure among those with a family history of prostate cancer (RR = 1.18 (95% CI 0.73, 1.82).

Conclusion—We find little evidence of an association between cumulative lifetime use of DDVP and risk of any cancer at this stage of follow up of the AHS.

Keywords

pesticides; organophosphate insecticides; dichlorvos (DDVP); prospective cohort; cancer etiology

INTRODUCTION

Dichlorvos or DDVP (2,2-Dichloroethenyl dimethylphosphate) is an organophosphate insecticide that has been in use in the United States and elsewhere since its registration in 1948. It is used for a variety of agricultural, commercial, industrial, and domestic purposes to control

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mushroom flies, aphids, spider mites, caterpillars, and other insects [1]. In agricultural applications, it is used on beef and dairy cattle, swine, sheep, poultry, other livestock, and around livestock buildings and on tobacco and greenhouse-grown food crops including lettuce, mushrooms, and tomatoes [2]. Because it is poisonous if swallowed, inhaled, or absorbed through the skin it has been used as a contact and stomach poison for control of insects in houses, campers, buildings, restaurants, garages, and various other areas [2,3] and in polyvinyl chloride resin strips worn by cats and dogs as collars for pet flea and tick control. About ten years ago, the U.S. Environmental Protection Agency (EPA) restricted use which curtailed certain domestic consumer uses [2,4].

The International Agency for Cancer Research (IARC) has classified DDVP as a possible (group 2B) human carcinogen [5] on the basis of significant increases of forestomach tumors in mice and leukemias and pancreatic acinar adenomas in rats as evaluated by the U.S. EPA and the National Toxicology Program [6,7]. Still, little is known about its carcinogenic effects on humans and the interpretation of the animal data is unclear [8]; differing animal strains and different routes of administration of the chemical have led to diverging conclusions about the carcinogenicity of DDVP. A recent study indicates that DDVP may inhibit the activity of natural killer cells, cytotoxic T lymphocytes and lymphokine-activated killer cells [9], which may provide plausibility to the leukemia findings in the aforementioned studies in rats. It is also of note that DDVP has been found to be positive in some in-vitro mutation assays [7] and may induce in-vivo mutagenicity via oxidative stress [10,11].

The epidemiologic literature has often implicated organophosphate compounds with increased risk of cancer but few have considered DDVP specifically. A case-control study from the Midwest indicated a suggestive elevated risk [12] of non-Hodgkin lymphoma associated with DDVP use. However, a pooled analysis that included three case-control studies found no association [13]. Early case reports linked DDVP exposure with leukaemogenic consequences, including acute lymphoblastic leukemia, in children [14]. A case-control study of leukemia among men in Iowa and Minnesota [15] found a significant two-fold risk associated with DDVP use and Flower et al. found that prenatal parental exposure to DDVP was associated with an increased risk of childhood cancer, (odds ratio (OR) = 2.06, 95 percent confidence interval (CI): 0.86, 4.90) [16]. Dichlorvos use has also been shown to increase prostate cancer risk in a California study of farm workers (OR= 1.35, 95 percent CI: 0.86, 4.90) [17] and in the Agricultural Health Study (AHS) of pesticide applicators in Iowa and North Carolina who have a family history of prostate cancer (OR= 1.92, 95 percent CI: 0.98, 3.75) [18]. These preliminary findings warrant a continued examination of DDVP exposure and its relationship to the incidence of all cancer and site specific cancer in the Agricultural Health Study.

MATERIALS AND METHODS

Study Population

The AHS is a prospective cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina and a detailed description of this cohort has been described elsewhere [19]. Briefly, applicators were recruited from December 1993 through December 1997. Participants completed a self-administered enrollment questionnaire which provided detailed exposure data, including information on the use of personal protective equipment, pesticide application methods, pesticide mixing, equipment repair, basic demographics and lifestyle exposures, family history of cancer, and information on 50 different pesticides, including DDVP. Cohort members were matched to cancer registry files in Iowa and North Carolina for case identification and to the state death registries and the National Death Index to ascertain vital status. Residence information was obtained from motor vehicle records, pesticide registration records, and address files of the Internal Revenue Service. Less than 2% of the cohort has been lost to follow-up by moving out of either state and 82.4% of the target population was

successfully recruited. This study includes all incident cancers diagnosed from enrollment (1993–1997) through December 31, 2004. Follow-up was censored at the time of participant death or movement out of state. All participants provided informed consent, and the protocol was approved by the institutional review boards of all appropriate institutions.

Exposure Assessment

Exposure to DDVP was quantified using information from a self-administered questionnaire. This questionnaire collected comprehensive-use data on 22 pesticides, including DDVP, and ever/never use information for 28 additional pesticides. Participants were asked how many years they applied DDVP (1yr or less, 2–5, 6–10, 11–20, 21–30, or more than 30 yrs.), how many days it was personally used in an average year (less than 5, 10–19, 20–39, 40–59, 60–150, and more than 150 days) and in what decade they first used DDVP (before 1960, in the 1960s, in the 1970s, in the 1980s, in the 1990s). Additional information was collected on a wide variety of exposures and lifestyle practices including: general information on pesticide application methods, personal protective equipment, pesticide mixing, equipment repair, alcohol intake, smoking history, family history of cancer in first degree relatives and other basic demographic characteristics. The questionnaires used for this analysis are the Phase I 'Enrollment Questionnaire,' the 'Farmer Applicator Questionnaire,' and the 'Commercial Applicator Questionnaire,' which can be accessed at http://aghealth.org/questionnaires.html.

We used an intensity-exposure algorithm to quantify pesticide exposure. Intensity levels were estimated using questionnaire data from enrollment and measurement data from the published pesticide exposure literature and the Pesticide Handlers Exposure Database [20], as follows: intensity level = [(mixing status + application method + equipment repair status) ×personal protective equipment use] [21]. Cumulative exposure days (CED) of DDVP use were calculated as [years of use × days per year]. CED were combined with the measure of intensity to create intensity-weighted cumulative exposure days (IWED) as follows: CED × intensity level. In order to optimize statistical power and to have sufficient cases numbers in each groups for adequate analysis, IWED was categorized into tertiles based on the distribution among all cancer cases into the following tertiles: <66, 66–589, and greater than 589. We also modeled CED and intensity level as two separate terms; results using CED and CED + intensity separately were similar to those for IWED thus we did not show cancer risk estimates for CED separately. To further explore the relationship between family history of prostate cancer and DDVP exposure, the top tertile was split at the median (589–1740, >1740) creating two equally distributed categories of exposure at the highest DDVP exposure levels (data not shown).

Data Analysis

Only first primary cancers were used in this analysis (n=2,943) thereby excluding 945 prevalent cases of cancer. Prevalent cases refer to those who had a cancer diagnosis before enrollment into the study. These cases had completed the enrollment questionnaire after a cancer diagnosis and have thus been excluded based on the potential for biased reporting of exposure or possible changes in use patterns due to previous cancer diagnosis. Applicators who did not provide information on DDVP exposure or were missing exposure algorithm information were excluded (n=6,314) as were subjects with missing information on age (n=2) or person-years of follow-up (n=288), leaving 49,762 individuals available for analysis. Poisson regression analysis was used to calculate rate ratios (RR) and 95% confidence intervals (95% CI) describing the effect of DDVP exposure on cancer incidence. A given cancer was evaluated if it had more than 10 exposed cases for IWED categories (prostate cancer, colon cancer, lung cancer, and all lymphohematopoietic cancers: leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma). Rate ratios were adjusted for confounding variables if the variable changed the parameter estimates by more than 10%; models for separate cancer sites differed based on this criterion. Factors evaluated for possible confounding, included age at

enrollment (<40, 40–49, 50–59, >= 60), state (North Carolina, Iowa), enrollment year, applicator type (commercial or private), education (high school or less, more than high school, missing), family history of any cancer in first-degree relatives (yes/no), family history of individual/given cancer for specific analyses (yes, no, missing), alcohol consumption during the past 12 months (ever, never, missing), cigarette smoking history (never, former smoker <5 pack-years, former smoker 5–30 pack-years, former smoker >30 pack-years, current smoker <15 pack-years, current smoker 15–45 pack-years, current smoker >45 pack-years), and two pesticides most highly correlated with DDVP based on cumulative exposure days, petroleum oil (Pearson correlation r =0.30), and chlordane (r =0.52) categorized by tertile of use. We used two reference groups to address uncontrolled confounding due to unmeasured differences between the exposed and unexposed applicators. These groups were: 1) those reporting no use or exposure to DDVP, and 2) those in the lowest exposure category (lowest tertile). Tests for trend were calculated using the midpoint value of each exposure category where it was treated as a continuous response in Poisson regression models. All p-values are two-sided and rate ratios and 95% confidence intervals were calculated using SAS statistical software (SAS Institute, Inc., Cary, North Carolina) from AHS data release version REL0612.

RESULTS

Characteristics of the study population are described in three categories in Table 1, 'Nonexposed', the lowest tertile of DDVP IWED or 'Lowest Exposed', and the top two tertiles of DDVP IWED or 'Highest Exposed'. A total of 4,613 applicators reported exposure to DDVP while 45,149 reported no exposure. Males constituted over 95% of subjects and private applicators over 90% of subjects in each exposure category. The nonexposed group differed on many factors compared with those in the lowest and highest exposed categories. Nonexposed applicators tended to be younger (37% <40yrs), reported current smoking more often (17%), reported less alcohol intake (32% never drink), had fewer years of formal education (42% beyond high school), were more likely to be from North Carolina (34%), and reported a family history of cancer less often compared with those exposed to DDVP. Highly exposed applicators tended to be slightly older (35% 40–49 yrs.) and reported current smoking less often (11%), current alcohol intake more often (76%), had more years of formal education (52% beyond high school), and tended to be from Iowa (90%) compared with those nonexposed to DDVP. As expected those in the highest exposed group reported a higher median number of cumulative days applying any pesticides (369.8 days) compared with lowest exposed and nonexposed (224.8 days).

Table 2 provides RRs and 95% CIs for selected cancers by intensity weighted exposure days of DDVP using nonexposed and lowest exposed referent groups for comparison. The incidence of all cancers combined was not associated with DDVP exposure and results for specific cancers also showed no significantly elevated rates. For prostate cancer, those in the highest exposure tertile had a nonsignificant reduced risk, RR=0.87 (95% CI 0.56, 1.36) compared with the lowest exposed referent group. A slightly increased but nonsignificant risk was observed for all lymphohematopoietic cancers when considering the highest tertile of exposure versus the lowest exposed as the referent, RR= 1.10 (95% CI 0.41, 2.96). Numbers of leukemia and NHL were too small for analysis, i.e., seven and six exposed cases, respectively.

Table 3 shows the effect of DDVP exposure by family history of prostate cancer. In the AHS, previous analyses have suggested an increased risk of prostate cancer associated with DDVP exposure but only among those with a family history of prostate cancer [18]. Those who reported ever being exposed to DDVP and had no family history of prostate cancer showed a small reduced risk of prostate cancer RR = 0.96 (95% CI 0.77, 1.21), while those with a family history of prostate cancer who reported ever using DDVP had a slightly increased risk, RR = 1.18 (95% CI 0.73, 1.82) though these are not significant. Those with no family history

generally had negligible or slightly reduced risks of prostate cancer (none are significant). Overall, there were no significant increased risks of prostate cancer among those reporting a family history of prostate cancer. After subdividing the top tertile of exposure at its median, some elevated risks are apparent among those with a family history but are based on small numbers (n=8, RR = 2.53, 95% CI 1.22, 5.24; data not shown).

DISCUSSION

In this study, we examined occupational DDVP exposure prior to enrollment as a risk factor for incident cancer diagnosed after enrollment. We did not observe significantly increased risks associated with DDVP use for any cancer in the AHS, which now includes incident cancers accrued through December 31, 2004. Previous epidemiologic investigations suggested a potential effect of DDVP on three specific cancer sites: prostate cancer [17,18], leukemia [15], and NHL [12]. We did not find evidence for an increased risk of any of these cancers associated with DDVP in this cohort.

Previous findings in the AHS cohort have implicated four other organophosphate compounds (fonofos, coumaphos, phorate, and chlorpyrifos) with increased risk of prostate cancer among those with a family history of prostate cancer [18,22]. A slight excess of prostate cancer was associated with ever use of DDVP, but this was among a smaller set of cases (n= 566 prostate cancer cases) [18]. The current analysis follows up on these previous findings using a total of 1,180 prostate cancer cases. Although relative risks tended to be elevated we did not observe a significant excess risk associated with DDVP exposure among those with a family history of prostate cancer in this analysis.

Most of the previous research on the health effects of DDVP focuses on its relationship with lymphohematopoietic cancers. IARC classifies DDVP as a possible human carcinogen based on the increased incidence of leukemia found in animal studies, while another study observed serious immune alterations associated with DDVP exposure [6,9]. Some epidemiologic investigations [9,15,16,23,24] have reported associations with lymphatic and hematopoietic cancers, but we see no evidence for an association here for lymphohematopoietic cancers as a group. Numbers of leukemia and NHL were too small for meaningful individual analyses.

The AHS cohort provides a unique opportunity to study DDVP-specific exposure and cancer risk. The collection of exposure information prior to the diagnosis of cancer eliminates a potential bias associated with retrospective studies. Information on pesticide use and detailed information on other occupational and lifestyle factors allows us to control for potential confounding from established risk factors and other pesticide exposures. Some limitations also need to be acknowledged. The numbers of exposed cases for less common cancers are small. In addition, the accuracy of self-reported factors has been found to be reasonably reliable in this particular cohort [25,26], however misclassification of pesticides undoubtedly occurs.

In summary, this is the largest study to specifically evaluate DDVP exposure and cancer risk, and it is the only prospective analysis. At this stage of follow up, our findings provide little evidence that exposure to DDVP is associated with the incidence of any cancer at this stage of follow up of the AHS cohort. The AHS cohort will continue to follow-up the association of DDVP with family history and prostate cancer. In addition, we will examine the association of DDVP and NHL and leukemia when sufficient cases become available for analysis.

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Abbreviations

DDVP	Dichlorvos
AHS	Agricultural Health Study
IWED	Intensity-Weighted cumulative Exposure Days
EPA	Environmental Protection Agency
IARC	International Agency for Cancer Research
OR	Odds Ratio
CI	Confidence Interval
RR	Rate Ratio

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Table 1

Characteristics of Applicators by Dichlorvos Exposure Category in the Agricultural Health Study[a]

Characteristic	Nonexposed		Lowest Exposed[b]		Highest Exposed[b]	
	No. (n=45,149)	%	No. (n=1,335)	%	No. (n=3,278)	%
Age						
<40	16,580	37	358	27	869	27
40–49	12,299	27	458	34	1,157	35
50–59	8,850	20	311	23	790	24
60+	7,420	16	208	16	462	14
Gender						
Male	43,917	97	1,317	99	3,246	99
Female	1,232	3	18	1	32	1
State of Residence						
Iowa	29,600	66	1,144	86	2,943	90
North Carolina	15,549	34	191	14	335	10
Applicator Type						
Private	40,978	91	1,224	92	3,077	94
Commercial	4,171	9	111	8	201	6
Smoking History						
Never	23,800	53	810	61	1,917	59
Former	13,097	29	384	29	969	30
Current	7,715	17	135	10	374	11
Missing	537	1	6	1	18	1
Current Alcohol Intake						
Never	14,248	32	318	24	762	23
Ever	30,287	67	1,005	75	2,499	76
Missing	614	1	12	1	17	1
Education						
High School/GED or less	25,095	56	490	37	1,518	46
Beyond High School	19,100	42	827	62	1,719	52
Missing	954	2	18	1	41	1

Characteristic	Nonexposed		Lowest Exposed[b]		Highest Exposed[b]	
	No. (n=45,149)	%	No. (n=1,335)	%	No. (n=3,278)	%
Family History of Cancer						
No	27,478	61	708	53	1,722	53
Yes	17,671	39	627	47	1,556	48
Median (range) no. of lifetime days applying pesticides	224.8 (0–7000)		224.8 (2.5–7000)		369.8 (2.5–7000)	
Median years of follow up[c]	9.74		9.78		9.07	

[a] Restricted to those without previous cancer diagnosis

[b] Lowest Exposed refers to the first tertile of exposure; Highest Exposed refers to the second and third tertile of exposure

[c] Follow-up through 2004 (range of follow-up years >0–11) Percents may not sum to 100 due to rounding

Table 2

Rate ratios for selected cancers by intensity-weighted DDVP exposure days among AHS participants[a,b]

Cancer Site	Intensity-weighted DDVP exposure days	Cases (n)	Nonexposed referent RR (95% CI)	Lowest Exposed referent RR (95% CI)
All cancers	No Exposure	2703	1.00	
	<66	74	0.92 (0.73, 1.15)	1.00
	66–589	85	0.81 (0.65, 1.01)	0.89 (0.65, 1.22)
	>589	81	0.92 (0.74, 1.15)	1.01 (0.74, 1.38)
	p for trend		0.42	0.82
Prostate[c]	No Exposure	1065	1.00	
	<66	40	1.13 (0.82, 1.56)	1.00
	66–589	38	0.85 (0.62, 1.18)	0.75 (0.48, 1.18)
	>589	37	0.99 (0.71, 1.37)	0.87 (0.56, 1.36)
	p for trend		0.88	0.84
Colon	No Exposure	192	1.00	
	<66	7	0.97 (0.43, 2.19)	1.00
	66–589	8	1.01 (0.50, 2.04)	1.04 (0.36, 2.99)
	>589	10	1.48 (0.78, 2.80)	1.53 (0.56, 4.21)
	p for trend		0.25	0.33
Lung[d]	No Exposure	277	1.00	
	<66	5	0.83 (0.34, 2.01)	1.00
	66–589	2	0.13 (0.02, 0.91)	0.15 (0.02, 1.31)
	>589	6	0.98 (0.43, 2.21)	1.18 (0.36, 3.88)
	p for trend		0.85	0.93
Lymphohematopoietic[e]	No Exposure	258	1.00	
	<66	7	0.91 (0.42, 1.95)	1.00
	66–589	8	0.75 (0.36, 1.55)	0.83 (0.30, 2.30)
	>589	10	1.00 (0.51, 1.96)	1.10 (0.41, 2.96)
	p for trend		0.98	0.51

Abbreviations (alphabetical): Agricultural Health Study (AHS); Confidence interval (CI); Dichlorvos (DDVP); Rate Ratio (RR)

[a] Follow-up through 2004

[b] Adjusted for age, enrollment year, chlordane, and petroleum oil

[c] Additionally adjusted for family history of prostate cancer and applicator type (commercial vs. private)

[d] Additionally adjusted for state of residence and smoking (never, pack-years among former smokers and pack-years among current smokers)

[e] Additionally adjusted for family history of hematopoietic cancers

Table 3

Rate Ratios for intensity-weighted DDVP exposure days by family history of prostate cancer in the AHS[a,b]

	Family History of Prostate Cancer			
	NO		YES	
	RR (95% CI)		RR (95% CI)	
Ever Exposed	**0.96 (0.77, 1.21)**		**1.18 (0.73, 1.82)**	
Intensity-weighted DDVP exposure days	**Cases (n)**	**RR (95% CI)**	**Cases (n)**	**RR (95% CI)**
No Exposure	813	1.00	176	1.00
<66	27	1.08 (0.73, 1.59)	11	1.29 (0.69, 2.40)
66–589	31	0.93 (0.65, 1.33)	7	0.72 (0.34, 1.55)
>589	26	0.90 (0.61, 1.33)	10	1.42 (0.75, 2.70)
p for trend		0.34		0.57

Abbreviations (alphabetical): Agricultural Health Study (AHS); Confidence interval (CI); Dichlorvos (DDVP); Rate Ratio (RR)

[a] Follow-up through 2004

[b] Adjusted for age, enrollment year, applicator type (commercial vs. private), chlordane, and petroleum oil